INTERNATIONAL STANDARD

ISO 5840-1

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Cardiovascular implants — Cardiac valve prostheses —

Part 1: General requirements

Implants cardiovasculaires — Prothèses valvulaires —

Partie 1: Exigences générales

Reference number
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ISO copyright office
Ch. de Blandonnet 8 • CP 401
CH-1214 Vernier, Geneva, Switzerland
Tel. +41 22 749 01 11
Fax +41 22 749 09 47
copyright@iso.org
www.iso.org

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Foreword

ISO (the International Organization for Standardization) is a worldwide federation of national standards bodies (ISO member bodies). The work of preparing International Standards is normally carried out through ISO technical committees. Each member body interested in a subject for which a technical committee has been established has the right to be represented on that committee. International organizations, governmental and non-governmental, in liaison with ISO, also take part in the work. ISO collaborates closely with the International Electrotechnical Commission (IEC) on all matters of electrotechnical standardization.

The procedures used to develop this document and those intended for its further maintenance are described in the ISO/IEC Directives, Part 1. In particular the different approval criteria needed for the different types of ISO documents should be noted. This document was drafted in accordance with the editorial rules of the ISO/IEC Directives, Part 2 (see www.iso.org/directives).

Attention is drawn to the possibility that some of the elements of this document may be the subject of patent rights. ISO shall not be held responsible for identifying any or all such patent rights. Details of any patent rights identified during the development of the document will be in the Introduction and/or on the ISO list of patent declarations received (see www.iso.org/patents).

Any trade name used in this document is information given for the convenience of users and does not constitute an endorsement.

For an explanation on the meaning of ISO specific terms and expressions related to conformity assessment, as well as information about ISO's adherence to the WTO principles in the Technical Barriers to Trade (TBT) see the following URL: Foreword - Supplementary Information

The committee responsible for this document is ISO/TC 150, *Implants for surgery*, Subcommittee SC 2, *Cardiovascular implants and extracorporeal systems.*

This first edition of ISO 5840-1, together with ISO 5840-2 and ISO 5840-3, cancels and replaces ISO 5840:2005, which has been technically revised.

ISO 5840 consists of the following parts, under the general title *Cardiovascular implants — Cardiac valve prostheses:*

— *Part 1: General requirements*

— *Part 2: Surgically implanted heart valve substitutes*

— *Part 3: Heart valve substitutes implanted by transcatheter techniques*

Introduction

There is, as yet, no heart valve substitute which can be regarded as ideal.

The ISO 5840–series has been prepared by a group well aware of the issues associated with heart valve substitutes and their development. In several areas, the provisions of the ISO 5840–series deliberately have not been specified to encourage development and innovation. It does specify the types of tests, test methods, and/or requirements for test apparatus and requires documentation of test methods and results. The areas with which the ISO 5840–series are concerned are those which will ensure that associated risks to the patient and other users of the device have been adequately mitigated, facilitate quality assurance, aid the clinician in choosing a heart valve substitute, and ensure that the device will be presented at the operating table in convenient form. Emphasis has been placed on specifying types of *in vitro* testing, on preclinical *in vivo* and clinical evaluations, on reporting of all *in vitro*, preclinical *in vivo*, and clinical evaluations, and on the labelling and packaging of the device. Such a process involving *in vitro*, preclinical *in vivo*, and clinical evaluations is intended to clarify the required procedures prior to market release and to enable prompt identification and management of any subsequent problems.

With regard to *in vitro* testing and reporting, apart from basic material testing for mechanical, physical, chemical, and biocompatibility characteristics, the ISO 5840–series also covers important hydrodynamic and durability characteristics of heart valve substitutes. The ISO 5840–series does not specify exact test methods for hydrodynamic and durability testing, but it offers guidelines for the test apparatus.

The ISO 5840–series is incomplete in several areas. It is intended to be revised, updated, and/or amended as knowledge and techniques in heart valve substitute technology improve.

Cardiovascular implants — Cardiac valve prostheses —

Part 1: General requirements

1 Scope

This part of ISO 5840 is applicable to heart valve substitutes intended for human implantation and provides general requirements. Subsequent parts of the ISO 5840–series provide specific requirements.

This part of ISO 5840 is applicable to both newly developed and modified heart valve substitutes and to the accessories, packaging, and labelling required for their implantation and for determining the appropriate size of the heart valve substitute to be implanted.

This part of ISO 5840 outlines an approach for qualifying the design and manufacture of a heart valve substitute through risk management. The selection of appropriate qualification tests and methods are derived from the risk assessment. The tests may include those to assess the physical, chemical, biological, and mechanical properties of heart valve substitutes and of their materials and components. The tests may also include those for preclinical *in vivo* evaluation and clinical evaluation of the finished heart valve substitute.

This part of ISO 5840 defines operational conditions for heart valve substitutes.

This part of ISO 5840 excludes homografts.

NOTE A rationale for the provisions of this part of ISO 5840 is given in Annex A.

2 Normative references

The following documents, in whole or in part, are normatively referenced in this document and are indispensable for its application. For dated references, only the edition cited applies. For undated references, the latest edition of the referenced document (including any amendments) applies.

ISO 5840-2, *Cardiovascular implants — Cardiac valve prostheses —Part 2: Surgically implanted heart valve substitutes*

ISO 5840-3, *Cardiovascular implants — Cardiac valve prostheses —Part 3: Heart valve substitutes implanted by transcatheter techniques*

ISO 11135, *Sterilization of health-care products — Ethylene oxide — Requirements for the development, validation and routine control of a sterilization process for medical devices*

ISO 11137 (all parts), *Sterilization of health care products — Radiation*

ISO 11607 (all parts), *Packaging for terminally sterilized medical devices*

ISO 14155, *Clinical investigation of medical devices for human subjects — Good clinical practice*

ISO 14160, *Sterilization of health care products — Liquid chemical sterilizing agents for single-use medical devices utilizing animal tissues and their derivatives — Requirements for characterization, development, validation and routine control of a sterilization process for medical devices*

ISO 14630:2012, *Non-active surgical implants — General requirements*

ISO 14937, *Sterilization of health care products — General requirements for characterization of a sterilizing agent and the development, validation and routine control of a sterilization process for medical devices*

ISO 14971, *Medical devices — Application of risk management to medical devices*

ISO 17665 (all parts), *Sterilization of health care products — Moist heat*

3 Terms and definitions

For the purposes of this document, the following terms and definitions apply.

3.1
accessories
device-specific tools that are required to assist in the implantation of the *heart valve substitute* (3.28)

3.2
adverse event
AE
untoward medical occurrence in a study subject which does not necessarily have to have a causal relationship with study treatment

Note 1 to entry: An AE can be an unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease, temporary or permanent, whether or not related to the prosthetic valve implantation or procedure.

3.3
actuarial methods
statistical technique for calculating event rates over time

Note 1 to entry: Standard actuarial methods calculate the probability of freedom from events within pre-specified intervals of time. When the intervals approach zero width, the methods are called Kaplan-Meier methods.

3.4
arterial end diastolic pressure
minimum value of the arterial pressure during diastole

3.5
arterial peak systolic pressure
maximum value of the arterial pressure during *systole* (3.63)

3.6
back pressure
differential pressure applied across the valve during the closed phase

3.7
body surface area
BSA
total surface area (m^2) of the human body

Note 1 to entry: This can be calculated (Mosteller's formula) as the square root of the product of the weight in kg times the height in cm divided by 3 600 (see Reference [31]).

3.8
cardiac index
cardiac output (3.9) (CO, L/min) divided by the *body surface area* (3.7) (BSA, m^2) with units L/min/m^2

3.9
cardiac output
CO
stroke volume (3.59) times heart rate

3.10
closing volume
portion of the *regurgitant volume* (3.48) that is associated with the dynamics of valve closure during a single *cycle* (3.15)

Note 1 to entry: See Figure 1.

3.11
coating
thin-film material that is applied to an element of a *heart valve system* (3.29) to modify its physical or chemical properties

3.12
compliance
relationship between change in diameter and change in pressure of a deformable tubular structure (e.g. valve annulus, aorta, conduit) defined in this part of ISO 5840 as

$$C = 100\% \times \frac{(r_2 - r_1) \times 100}{r_1 \times (p_2 - p_1)}$$

where

C is the compliance in units of % radial change/100 mmHg;

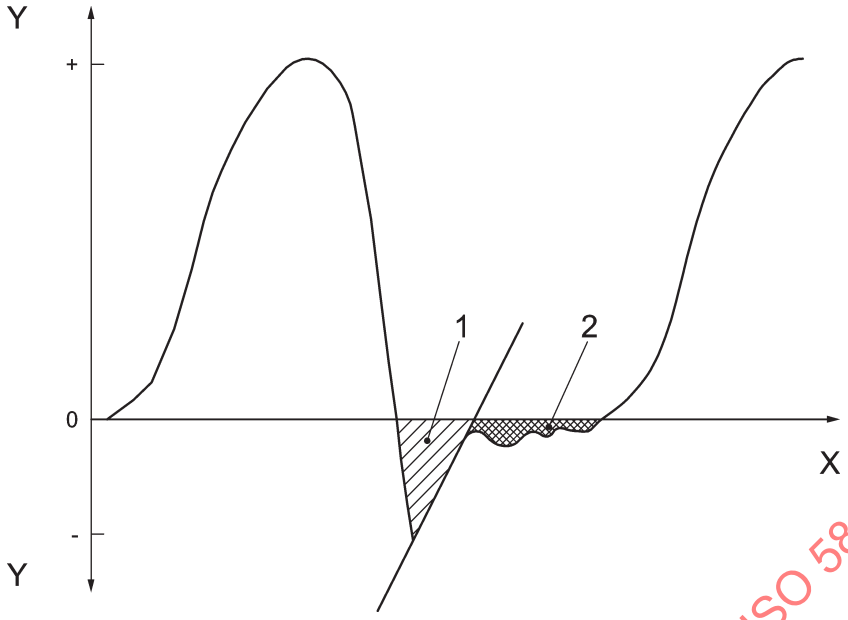
p_1 is the diastolic pressure, in mmHg;

p_2 is the systolic pressure, in mmHg;

r_1 is the inner radius at p_1, in millimetres;

r_2 is the inner radius at p_2, in millimetres.

Note 1 to entry: Reference ISO 25539-1.



Key

X time
Y flowrate
1 closing volume
2 leakage volume

Figure 1 — Schematic representation of flow waveform and regurgitant volumes for one cycle

3.13
component-joining material
material such as a suture, adhesive, or welding compound used to assemble the components of a *heart valve system* (3.29)

3.14
cumulative incidence
statistical technique where events other than death can be described by the occurrence of the event over time without including death of the subjects

Note 1 to entry: Cumulative incidence is also known as “actual” analysis.

3.15
cycle
one complete sequence in the action of a *heart valve substitute* (3.28) under pulsatile-flow conditions

3.16
cycle rate
number of complete *cycles* (3.15) per unit of time usually expressed as cycles per minute (cycles/min)

3.17
design verification
establishment by objective evidence that the design output meets the design input requirements

3.18
design validation
establishment by objective evidence that device specifications conform with user needs and *intended use(s)* (3.31)

3.19
device embolization
dislodgement from the intended and documented original position to an unintended and non-therapeutic location

3.20
device failure
inability of a device to perform its intended function sufficient to cause a hazard

3.21
device migration
detectable movement or displacement of the *heart valve substitute* (3.28) from its original position within the *implant position* (3.30) and without *device embolization* (3.19)

3.22
effective orifice area
EOA
orifice area that has been derived from flow and pressure or velocity data

For *in vitro* testing, EOA is defined as: $\mathrm{EOA} = \dfrac{q_{V\,\mathrm{RMS}}}{51{,}6 \times \sqrt{\dfrac{\Delta p}{\rho}}}$

where

EOA is the Effective Orifice Area (cm^2);

$q_{V_{\mathrm{RMS}}}$ is the root mean square forward flow (ml/s) during the positive differential pressure period;

Δp is the mean pressure difference (measured during the positive differential pressure period) (mmHg);

ρ is the density of the test fluid (g/cm^3).

Note 1 to entry: See 3.53.

3.23
failure mode
mechanism of *device failure* (3.20)

Note 1 to entry: Support structure fracture, calcification, and prolapse are examples of failure modes.

3.24
flexible surgical heart valve substitute
surgical heart valve substitute (3.62) wherein the *occluder* (3.40) is flexible under physiological conditions

Note 1 to entry: The orifice ring may or may not be flexible.

3.25
follow-up
continued assessment of patients who have received the *heart valve substitute* (3.28)

3.26
forward flow volume
volume of flow ejected through the *heart valve substitute* (3.28) in the forward direction during one *cycle* (3.15)

3.27
fracture
complete separation of any structural component of the *heart valve substitute* (3.28) that was previously intact

3.28
heart valve substitute
device used to replace the function of a natural valve of the heart

3.29
heart valve system
implantable device, *accessories* (3.1), packaging, labelling, and instructions

3.30
implant site/implant position
intended location of *heart valve substitute* (3.28) implantation or deployment

3.31
intended use
use of a product or process in accordance with the specifications, instructions, and information provided by the manufacturer

3.32
Kaplan-Meier methods
statistical approaches for calculating event rates over time when the actual dates of events for each person in the population are known

3.33
leakage volume
portion of the *regurgitant volume* (3.48) which is associated with leakage during the closed phase of a valve in a single *cycle* (3.15) and is the sum of the *transvalvular leakage volume* (3.66) and *paravalvular leakage volume* (3.43)

Note 1 to entry: The point of separation between the closing and leakage volumes is obtained according to a defined and stated criterion (the linear extrapolation shown in Figure 1 is just an example).

3.34
linearized rate
total number of events divided by the total time under evaluation

Note 1 to entry: Generally, the rate is expressed in terms of percent per patient year.

3.35
major bleeding
any episode of major internal or external bleeding that causes death, hospitalization, or permanent injury (e.g. vision loss) or necessitates transfusion

3.36
major paravalvular leak
paravalvular leakage leading to death or reintervention, or causing heart failure requiring additional medication, or causing moderate or severe regurgitation or prosthesis “rocking” on investigation even in the apparent absence of symptoms, or causing hemolytic anemia

3.37
mean arterial pressure
time-averaged arithmetic mean value of the arterial pressure during one *cycle* (3.15)

3.38
mean pressure difference/mean pressure gradient
time-averaged arithmetic mean value of the pressure difference across a *heart valve substitute* (3.28) during the positive differential pressure period of the *cycle* (3.15)

3.39
nonstructural valve dysfunction
abnormality extrinsic to the *heart valve substitute* (3.28) that results in stenosis, regurgitation, and/or haemolytic anemia

3.40
occluder/leaflet
component that inhibits backflow

3.41
outflow tract profile height
maximum distance that the *heart valve substitute* (3.28) extends axially into the outflow tract in the open or closed position, whichever is greater, measured from the valve structure intended to mate with the top (atrial or aortic/pulmonic side) of the patient's annulus

3.42
pannus
ingrowth of tissue onto the *heart valve substitute* (3.28) which can interfere with normal functioning

3.43
paravalvular leakage volume
portion of the *leakage volume* (3.33) that is associated with leakage around the closed heart valve substitute during a single *cycle* (3.15)

3.44
profile height
maximal axial dimension of a *heart valve substitute* (3.28) in the open or closed position, whichever is greater

3.45
prosthetic valve endocarditis
any infection involving a prosthetic valve based on reoperation, autopsy, or the Duke Criteria for endocarditis

3.46
reference valve
heart valve substitute (3.28) with a known clinical experience used for comparative preclinical and clinical evaluations

3.47
regurgitant fraction
regurgitant volume (3.48) expressed as a percentage of the *forward flow volume* (3.26)

3.48
regurgitant volume
volume of fluid that flows through a *heart valve substitute* (3.28) in the reverse direction during one *cycle* (3.15) and is the sum of the *closing volume* (3.10) and the *leakage volume* (3.33)

Note 1 to entry: See Figure 1.

3.49
rigid surgical heart valve substitute
surgical heart valve substitute (3.62) wherein the *occluder(s)* (3.40) and orifice ring are non-flexible under physiological conditions

3.50
risk
combination of the probability of occurrence of harm and the *severity* (3.55) of that harm

[SOURCE: ISO 14971, 2.16]

3.51
risk analysis
systematic use of available information to identify hazards and to estimate the associated *risks* (3.50)

[SOURCE: ISO 14971, 2.17]

3.52
risk assessment
overall process comprising a *risk analysis* (3.51) and a risk evaluation

[SOURCE: ISO 14971, 2.18]

3.53
root mean square forward flow
RMS forward flow
square root of the integral of the volume flow rate waveform squared during the positive differential pressure interval of the forward flow phase used to calculate EOA

Note 1 to entry: Defining the time interval for flow and pressure measurement as the positive pressure period of the forward flow interval for EOA computation provides repeatable and consistent results for comparison to the minimum device performance requirements.

Note 2 to entry: This is calculated using the following equation:

$$q_{V_{\mathrm{RMS}}} = \sqrt{\frac{\int_{t_1}^{t_2} q_V(t)^2 dt}{t_2 - t_1}}$$

where

$q_{V_{\mathrm{RMS}}}$ is root mean square forward flow during the positive differential pressure period;

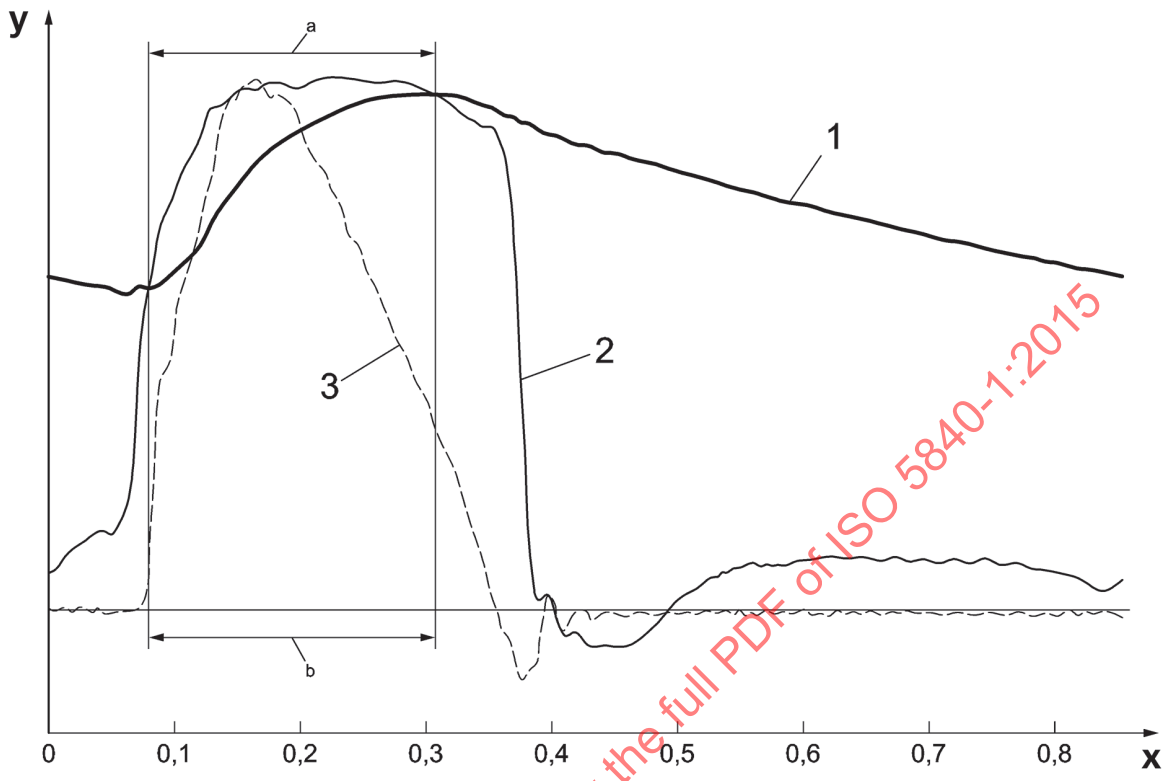
$q_V(t)$ is instantaneous flow at time (t);

t_1 is time at start of positive differential pressure period;

t_2 is time at end of positive differential pressure period.

Note 3 to entry: The rationale for use of $q_{V_{\mathrm{RMS}}}$ is that the instantaneous pressure difference is proportional to the square of instantaneous flow rate and it is the *mean pressure difference* (3.38) that is required.

Note 4 to entry: See Figure 2.



Key

1 aortic pressure
2 left ventricle pressure
3 aortic flow rate
X time (sec)
Y pressure (mmHg) and flow (L/min)
a Positive pressure range.
b $q_{V_{\mathrm{RMS}}}$ range.

Figure 2 — Schematic representation of the positive pressure period of an aortic forward flow interval

3.54
safety
freedom from unacceptable risk

[SOURCE: ISO 14971, 2.24]

3.55
severity
measure of the possible consequences of a hazard

[SOURCE: ISO 14971, 2.25]

3.56
simulated cardiac output
forward flow volume (3.26) times heart rate

3.57
sterility assurance level
SAL
probability of a single viable microorganism occurring on an item after *sterilization* (3.58)

Note 1 to entry: The term SAL takes a quantitative value, generally 10^{-6} or 10^{-3}. When applying this quantitative value to assurance of sterility, an SAL of 10^{-6} has a lower value, but provides a greater assurance of sterility than an SAL of 10^{-3}.

[SOURCE: ISO/TS 11139, 2.46]

3.58
sterilization
validated process used to render a product free from viable microorganisms

Note 1 to entry: In a sterilization process, the rate of microbial inactivation is exponential and thus, the survival of a microorganism on an individual item can be expressed in terms of probability. While this probability can be reduced to a very low number, it can never be reduced to zero.

Note 2 to entry: See 3.57.

[SOURCE: ISO/TS 11139:2006]

3.59
stroke volume
SV
volume of blood pumped by a ventricle in one contraction

3.60
structural valve deterioration
change in the function of a *heart valve substitute* (3.28) resulting from an intrinsic abnormality that causes stenosis or regurgitation

Note 1 to entry: This definition excludes infection or thrombosis of the heart valve substitute. It includes intrinsic changes such as wear, fatigue failure, stress fracture, occluder escape, suture line disruption of components of the prosthesis, calcification, cavitation erosion, leaflet tear, and stent creep.

3.61
support structure
component of a *heart valve substitute* (3.28) that houses the *occluder(s)* (3.40) (e.g. stent, frame, housing)

3.62
surgical heart valve substitute
heart valve substitute (3.28) generally requiring direct visualization and cardiopulmonary bypass for implantation

3.63
systolic duration
systole
portion of cardiac cycle time corresponding to ventricular contraction

Note 1 to entry: See Figure 3.

3.64
thromboembolism
embolic event involving clot that occurs in the absence of infection

Note 1 to entry: Thromboembolism may be manifested by a neurological event or a noncerebral embolic event.

3.65
transcatheter heart valve substitute
heart valve substitute (3.28) delivered through a catheter and implanted in a manner generally not involving direct visualization and generally involving a beating heart

3.66
transvalvular leakage volume
component of the *leakage volume* (3.33) that is associated with leakage through the closed valve during a single *cycle* (3.15)

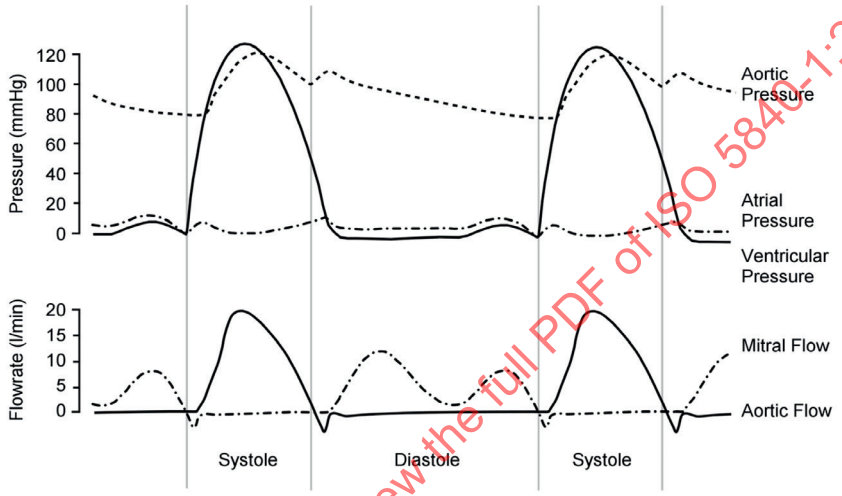


Figure 3 — Wiggers Diagram, showing various events of a cardiac cycle

3.67
usability
characteristic of the user interface that establishes effectiveness, efficiency, ease of user learning and user satisfaction

4 Abbreviations

For the purposes of this document, the following abbreviations apply.

AE Adverse Event

AF Atrial Fibrillation

AWT Accelerated Wear Testing

BSA Body Surface Area

ECG Electrocardiogram

EOA Effective Orifice Area

FEA Finite Element Analysis

IEC	International Electrotechnical Commission
IFU	Instructions For Use
IOD	Internal Orifice Diameter
LV	Left Ventricle, Left Ventricular
MAP	Mean Arterial Pressure
MRI	Magnetic Resonance Imaging
RV	Right Ventricle, Right Ventricular

5 Fundamental requirements

The manufacturer shall determine, at all stages of the product life cycle, the acceptability of the product for clinical use.

6 Device description

6.1 Intended use

The manufacturer shall identify the physiological condition(s) to be treated, the intended patient population, potential adverse events, and intended claims.

6.2 Design inputs

6.2.1 Operational specifications

The manufacturer shall define the operational specifications for the device including the principles of operation, intended device delivery approach/process, expected device lifetime, shelf life, shipping/storage limits, and the physiological environment in which it is intended to function. The manufacturer shall carefully define all relevant dimensional parameters that will be required to accurately select the size of device to be implanted. Table 1 and Table 2 define the expected physiological parameters of the intended adult patient population for heart valve substitutes for both normal and pathological patient conditions.

Refer to Annex E for *in vitro* test guidelines for paediatric devices.

6.2.2 Performance specifications

The manufacturer shall establish (define, document, and implement) the clinical performance requirements of the device and the corresponding device performance specifications for the intended use and device claims. The specific performance specifications are provided in ISO 5840-2 and ISO 5840-3.

6.2.3 Implant procedure

The entire system shall provide intended users the ability to safely and effectively perform all required pre-operative, intra-operative, and post-operative procedural tasks and achieve all desired objectives. This shall include all other device specific tools and accessories that intended users will use to complete the procedure.

NOTE For guidance on how to determine and establish design attributes pertaining to the use of the system to conduct the implant procedure, see IEC 62366.

Table 1 — Heart valve substitute operational environment for left side of heart — Adult population

Parameter	General condition			
Surrounding medium	Human heart/Human blood			
Temperature	34 °C to 42 °C			
Heart rate	30 bpm to 200 bpm			
Cardiac output	3 L/min to 15 L/min			
Forward flow volume	25 mL to 100 mL			
Blood pressures and resultant pressure loads by patient condition	Arterial peak systolic pressure mmHg	Arterial end diastolic pressure mmHg	Peak differential pressure across closed valves[a]	
			Aortic ΔP_A mmHg	Mitral ΔP_M mmHg
Normotensive	120	80	100	120
Hypotensive	60	40	50	60
Hypertensive				
Mild	140 to 159	90 to 99	115 to 129	140 to 159
Moderate	160 to 179	100 to 109	130 to 144	160 to 179
Severe	180 to 209	110 to 119	145 to 164	180 to 209
Very Severe	≥210	≥120	≥165	≥210

[a] Peak differential pressure across closed aortic valve estimated clinically using the following relationship:

— $\Delta P_A \approx$ pressure associated with dicrotic notch assuming LV pressure is zero ≈ Arterial End Diastolic Pressure + 1/2(Arterial Peak Systolic Pressure – Arterial End Diastolic Pressure).

— Peak differential pressure across closed mitral valve estimated to be equivalent to Arterial Peak Systolic Pressure.

6.2.4 Packaging, labelling, and sterilization

The heart valve system shall meet the requirements for packaging, labelling, and sterilization contained within Annex B, Annex C, and Annex D, respectively.

The manufacturer shall provide sufficient information and guidance in the labelling to allow for appropriate preparation of the implant site, accurate selection of appropriate implant size, and reliable implantation of the heart valve substitute.

6.3 Design outputs

The manufacturer shall establish (i.e. define, document, and implement) a complete specification of the heart valve system including component and assembly-level specifications, delivery system (if applicable), accessories, packaging, and labelling. In addition to the physical components of the heart valve system, the implant procedure itself should be considered an important element of safe and effective heart valve therapy.

Table 2 — Heart valve substitute operational environment for right side of heart — Adult population

Parameter	General Condition			
Surrounding medium	Human heart/Human blood			
Temperature	34 °C to 42 °C			
Heart rate	30 bpm to 200 bpm			
Cardiac output	3 L/min to 15 L/min			
Forward flow volume	25 mL to 100 mL			
Blood pressures and resultant pressure loads by patient condition	Right ventricle peak systolic pressure mmHg	Pulmonary artery end diastolic pressure mmHg	Peak differential pressure across closed valve [a]	
			Pulmonary ΔP_P mmHg	Tricuspid ΔP_T mmHg
Normotensive	18 to 35	8 to 15	13 to 25	18 to 35
Hypotensive	15	5	10	15
Hypertensive				
Mild	40 to 49	15 to 19	28 to 34	40 to 49
Moderate	50 to 59	20 to 24	35 to 42	50 to 59
Severe	60 to 84	25 to 34	43 to 59	60 to 84
Very Severe	≥85	≥35	≥60	≥85

[a] Peak differential pressure across closed pulmonic valve estimated clinically using the following relationship:

— ΔP_P approximately pressure associated with dicrotic notch assuming RV pressure is zero approximately Pulmonary Artery End Diastolic Pressure + 1/2(Right Ventricle Peak Systolic Pressure –Pulmonary Artery End Diastolic Pressure).

— Peak differential pressure across closed tricuspid valve estimated to be equivalent to Right Ventricle Peak Systolic Pressure.

6.4 Design transfer (manufacturing verification/validation)

The manufacturer shall generate a flowchart identifying the manufacturing process operations and inspection steps. The flowchart shall indicate the input of all components and important manufacturing materials.

As part of the risk management process, the manufacturer shall establish the control measures and process conditions necessary to ensure that the device is safe and suitable for its intended use. The risk management file shall identify and justify the verification activities necessary to demonstrate the acceptability of the process ranges chosen.

The manufacturer shall establish the adequacy of full scale manufacturing by validation of the manufacturing process. The manufacturer shall validate all special processes and process software and document the results of the validation.

NOTE See ISO 13485.

6.5 Risk management

The manufacturer shall define and implement a risk management program in accordance with ISO 14971.

7 Design verification testing and analysis/design validation

7.1 General requirements

The manufacturer shall perform verification testing to demonstrate that the device specifications result in a heart valve system that meets the design specifications (design output meets design input). The manufacturer shall establish tests relating to hazards identified from the risk analysis. The protocols shall identify the test purpose, setup, equipment (specifications, calibration, etc.), test conditions (with a justification of appropriateness to anticipated *in vivo* operating conditions for the device), acceptance criteria, and sample quantities tested.

The manufacturer shall validate the design of the heart valve system.

7.2 *In vitro* assessment

Reference the following Annexes for *in vitro* assessments:

— Annex F: Statistical procedures when using *in vitro* performance criteria;

— Annex G: Examples and definitions of some physical and material properties of heart valve systems;

— Annex H: Examples of standards applicable to testing of materials and components of heart valve systems;

— Annex I: Raw and post-conditioning mechanical properties for support structure materials;

— Annex J: Corrosion assessment;

Specific requirements for *in vitro* assessments are provided in ISO 5840-2 and ISO 5840-3.

7.3 Preclinical *in vivo* evaluation

A preclinical *in vivo* test program shall be conducted in order to address the heart valve system, placement, imaging characteristics, and safety and performance. The preclinical program design should be based on risk management assessment. The specific preclinical requirements are provided in ISO 5840-2 and ISO 5840-3.

7.4 Clinical investigations

For new heart valve designs, a clinical investigation shall be carried out in accordance with the ISO 5840-series. For modification of an existing valve, a clinical investigation shall be considered based on the results of a risk assessment that evaluates the modification. The clinical investigation shall be conducted in accordance with ISO 14155.

If a determination is made that clinical investigations are not required, justification shall be documented in the risk management file. Reference the following text for clinical assessments:

— Annex K: Echocardiographic protocol;

— ISO 5840-2 and ISO 5840-3 for specific clinical investigation requirements.

Annex A
(informative)

Rationale for the provisions of this part of ISO 5480

A.1 Rationale for risk-based approach

The rationale for basing this part of ISO 5840 on risk management is that the traditional requirements-based model cannot keep up with the speed of technological innovation. With the requirements-based model, manufacturers have to spend their time looking for ways to comply with the requirements of the standard rather than on developing new technologies that could lead to inherently safer products. The risk-based model challenges the manufacturer to continually evaluate known and theoretical risks of the device to develop the most appropriate methods for reducing the risks of the device and to implement the appropriate test and analysis methods to demonstrate that the risks have been reduced.

This part of ISO 5840 combines a requirement for implementing the risk-based model with best practice methods for verification testing appropriate to heart valve system evaluation. The intent of the risk assessment is to identify the hazards along with the corresponding failure modes and causes in order to identify the requisite testing and analysis necessary to evaluate the risk associated with each specific hazard. The risk management process provides the opportunity for the manufacturer to evaluate the best practice methods included within this part of ISO 5840. The manufacturer may choose to follow the best practice method as defined within this part of ISO 5840 or may deviate from the method and provide a scientific justification for doing so. The risk management file required by ISO 14971 should document these decisions with rationale.

The risk-based model requires a collaborative environment between the device developer (the manufacturer) and the body responsible for verifying compliance with the applicable regulation regarding safety and performance of the device. The manufacturer should strive for continuous improvement in device design, as well as test methodologies that can ensure safety and performance of a device with less reliance on years of patient experience for evidence of effectiveness.

A.2 Rationale for preclinical *in vivo* evaluation

The overall objective of preclinical *in vivo* evaluation is to test the safety and function of the heart valve system in a biological environment with the closest practically feasible similarity to human conditions.

The preclinical *in vivo* evaluation is the final investigational step prior to human implantation. Therefore, it should provide the regulatory body with an appropriate level of assurance that the heart valve system will perform safely.

No single uniformly acceptable animal model has been established. Therefore, the animal model(s) selected should be properly justified in order to ensure the highest degree of human compatible conditions for the heart valve system pertinent to the issues being investigated. Since chronic studies are conducted to elucidate heart valve substitute haemodynamic performance, biological responses, structural integrity, and delivery system and valve-related pathology in a specific anatomical position, it is preferable to undertake this longer-term testing of the valves in anatomical positions for which it is intended.

The concurrent implantation of reference heart valve substitutes enhances the comparative assessment by providing a bridge to known clinical performance. In addition, such an approach facilitates the distinction between the complications related to the reference heart valve substitute versus those of the test heart valve system.

A.3 Rationale for design verification and design validation testing

Verification and validation testing includes materials testing, preclinical bench testing, preclinical *in vivo* evaluation, and clinical investigations. Although clinical investigations are usually considered to be part of design validation, some of the requirements established under design input might be verifiable only under clinical conditions. The tests specified herein do not purport to comprise a complete test program. A comprehensive test program for the heart valve system should be defined as part of the risk assessment activities. Where the manufacturer's risk assessment concludes that the safety and performance will be better demonstrated by other tests or by modifying the test methods included in this standard, the manufacturer should include in the risk assessment a justification of the equivalence or superiority of the alternative test or test method.

The manufacturer should validate the design of the heart valve system, its packaging, labelling, and accessories. For a new heart valve system, design validation typically occurs in two phases. In the first phase, the manufacturer reviews the results of all verification testing and the manufacturing process validation prior to the first human implant. The review might also include analysis of the scientific literature, opinions of clinicians and other experts who will be using the device, and comparisons to historical evidence from similar designs. The output of the review should be that the device is safe and suitable for human clinical investigations. The second phase of design validation occurs in conjunction with the outcomes of the pre-marketing approval of the clinical investigation. The data from the approval phase clinical investigation should be reviewed to ensure that the device, its packaging, labelling, and accessories are safe and suitable for their intended use and ready for market approval. These validation activities should be documented.

For a modification to an existing heart valve system design or manufacturing method, the concepts of verification and validation continue to be applicable, but might be limited in scope. The risk analysis should define the scope of the verification and validation.

The use of clinical grade materials and components as opposed to generic test samples is important since fillers, additives, and processing aids can have profound implications on material properties. Testing should be designed to evaluate areas where materials are joined (e.g. welded, sutured, or glued) since these are potential areas for failure.

A.4 Rationale for echocardiographic assessment

Echocardiography is presently accepted as a practical and available method for evaluating human cardiac function and the function of heart valve substitutes. The accuracy of these diagnostic procedures depends upon the skill of the operator. All investigating institutions involved in the clinical evaluation of a specific heart valve substitute should employ the same echocardiographic protocol.

A.5 Rationale for clinical evaluation reporting

A heart valve system undergoing clinical evaluation should function as intended with valve complication rates within broadly acceptable performance criteria limits. To enable appropriate risk assessment, pre-operative, peri-operative, and follow-up data should be collated, analysed, and reported.

The clinical evaluation of a heart valve system requires documentation of specified complications. A new or modified heart valve system should perform as well as or better than existing heart valve systems. Where appropriate, randomized clinical trials should be conducted comparing the new heart valve system against existing heart valve systems and/or medical therapy. The clinical evaluation also requires formal statistical evaluation of the clinical data. Unanticipated valve-related complications will be reported and evaluated prior to the completion of the formal methods of overall performance evaluation. Statistical evaluation methods and assessment criteria of clinical data could be different between paediatric and adult study populations. Given the perceived risks associated with heart valve systems, post-market surveillance protocols should be established.

A.6 Rationale for device sizing within labelling and instructions for use

In the past, problems have been reported with the labelling and instructions for use associated with size designations and sizing procedures for replacement heart valves. This has led to confusion among users about which size valve to implant in a particular patient. This has also led to confusion about how to compare results (published or otherwise) from one valve model to another. A solution to the problem can be achieved by providing more complete and accurate sizing information with respect to the anatomic position of the device (e.g. intra-annular, supra-annular for surgical valves) which will ultimately benefit the clinician and the patient.

A.7 Rationale for Human Factors Engineering

Manufacturers should incorporate Human Factors Engineering in accordance with IEC 62366 into their overall product development process in order to ensure the design and development of safe, effective, and easy-to-use heart valve systems.

Annex B
(normative)

Packaging

B.1 Requirements

The requirements of ISO 14630:2012, Clause 10 and the requirements of ISO 11607 shall apply.

B.2 Principle

Packaging shall be designed to ensure that the user is provided with a heart valve system whose characteristics and performance are unaltered by normal transit or storage. The packaging shall maintain the characteristics and performance of the package contents under normal conditions of handling, transit, and storage and shall permit the contents to be presented for use in an aseptic manner. If necessary, based on risk assessment, there shall be a means to show if the packaging was exposed to abnormal conditions (e.g. freezing, excessive heat, container damage) during transit or storage that damaged the heart valve system.

B.3 Containers

B.3.1 Unit container(s)

The heart valve system shall be packaged in unit container(s) designed so that any damage to the unit container(s) seal is readily apparent. The unit container(s) shall meet the requirements of ISO 11607.

B.3.2 Outer container

The unit container(s) shall be packaged in an outer container(s) (sales/storage package) to protect the unit container(s).

Annex C
(normative)

Product labels, instructions for use, and training

C.1 General

The requirements of ISO 14630:2012, Clause 11 shall apply.

Labels, instructions for use, and training programs shall be designed to ensure that the user is provided with information on handling and implanting the heart valve substitute and shall be approved and reviewed as part of the risk and quality management systems. Labels and instructions for use shall meet country-specific language requirements. Labelling of prosthetic cardiac valves that have been on the market before the current International Standard version shall be adapted to conform to current standards.

C.1.1 Unit-container label

Each unit container shall be marked with at least the following information:

— name or trade name;

— model number;

— serial/lot number;

— size and device type, if applicable (e.g. 21 mm, Aortic);

— word “Sterile” if applicable and the method of sterilization;

— for sterile devices, the use by date or the expiration date;

— statement regarding single use only (if applicable);

— reference to see instructions for use for user information.

C.1.2 Outer-container label

In addition to applicable storage instructions, each outer container shall be marked with at least word(s), phrase(s), and/or symbol(s) for the following:

— name or trade name of device;

— name, address, and phone number of manufacturer and/or distributor and other methods of contacting the manufacturer (e.g. facsimile number, email address). It might also be necessary to have the name and address of the importer established within the importing country or an authorized representative of the manufacturer established within the importing country;

— model number;

— serial/lot number;

— size and device type, if applicable (e.g. 21 mm, Aortic);

— net contents;

— the word “Sterile” and method of sterilization if applicable;

— for sterile devices, the use by date or the expiration date;

— statement regarding single use only (if applicable);

— devices intended for clinical investigations shall bear identification that the device is intended for investigational use only;

— any special storage or handling conditions as indicated in the device specification;

— warning against use of the device if the unit container has been opened or damaged;

— reference to see instructions for use for user information.

C.1.3 Instructions for use

Each heart valve system shall be accompanied by instructions for use that shall include at least the following:

— name or trade name of device;

— name, address, and phone number of manufacturer and/or distributor and other methods of contacting the manufacturer (e.g. facsimile number, email address). It might also be necessary to have the name and address of the importer established within the importing country or an authorized representative of the manufacturer established within the importing country;

— revision level of IFU and implementation date;

— net contents;

— indications for use and any known contraindications;

— device description including available models and user required dimensions (e.g. profile height, outflow tract profile height, valve size, external sewing ring diameter, internal orifice diameter);

— a description of any accessories required and reference to their instructions for their use;

— how the device is packaged/supplied;

— the word “Sterile” and method of sterilization if applicable;

— statement that the device can or cannot be resterilized;

— statement regarding single use only (if applicable);

— devices intended for clinical investigations shall bear identification that the device is intended for investigational use only;

— any special storage or handling conditions;

— warning against use of the device if the unit container has been opened or damaged;

— any warnings regarding handling or implanting the device;

— any other warnings or precautions specific for the device including, but not limited to concomitant procedures of use with other devices;

— instructions for resterilization (if applicable) including the maximum number of resterilization cycles, parameters which have been proven to be capable of achieving sterility of the device, and appropriate information relevant to other methods, apparatus, containers, and packaging;

— specific instructions for device preparation (i.e. rinsing requirements for tissue valves);

— specific instructions for implanting or using the device;

— specific instructions for sizing target implant site and selecting appropriate device size;

— list of potential complications;

— summary of clinical experience if required;

— the appropriate MR Safety designation (MR Conditional, MR Safe, or MR Unsafe) and a statement regarding MRI compatibility;

— any information or instructions which are intended to be communicated from the physician to the patient.

C.1.4 Labels for medical records

The manufacturer shall provide peel-off, self-adhering labels, or equivalent with each heart valve system that enables transfer of device information to the appropriate records. Each label shall contain the name or model designation, size, and serial number of the heart valve substitute and manufacturer identification.

The size of the labels shall be sufficient to display the required information in a legible format. The number of required labels may vary based on individual country policies.

C.2 Training for physicians and support staff

If it is required by the risk assessment, the manufacturer shall establish a structured training program for the physician and staff who will be involved in the peri-procedural care of the patient. The training program shall be designed to provide the physician and staff with the information and experience necessary to control user-associated risks when the device is used in accordance with the instructions for use. Training records shall be maintained as evidence that physicians have received appropriate training.

The training programme shall include the following elements where appropriate:

a) Description of all system components, as well as a summary of the basic principle of operation.

b) Complete review of the instructions for use including the indications for use, patient selection, contraindications, precautions, warnings, potential adverse events, pre-procedure setup, sizing the valve, implant procedure, and post-procedure patient care.

c) Review of imaging modalities that can be used for implanting the device.

d) Hands-on bench top demonstration of the heart valve system in a simulated model.

e) Use of the device in an animal model or other appropriate models such as a robotic simulation system.

f) A clinical training program including proctored cases.

g) User verification/validation determined by predefined criteria.

Annex D
(normative)

Sterilization

The requirements of ISO 14630:2012, Clause 9 shall apply together with the following.

For devices or accessories supplied sterile, sterilization shall occur by an appropriate method and shall be validated in accordance with internationally recognized criteria as specified in ISO 17665, ISO 11135, ISO 11137, ISO 14160, and ISO 14937. If the manufacturer states that the heart valve system can be resterilized prior to implantation, adequate instructions shall be provided by the manufacturer including parameters that have been proven to be capable of achieving sterility of the device.

For any reusable devices or accessories, the instructions for use shall contain information on the appropriate processes to allow reuse including cleaning, disinfection, packaging, and, where appropriate, the method of sterilization and any restriction on the number of reuses.

Annex E
(informative)

In vitro test guidelines for paediatric devices

E.1 General and paediatric definitions

Traditionally, heart valve systems have been designed, tested, and labelled for the adult population. Many real and perceived scientific, marketing, and regulatory barriers have limited the development of paediatric heart valve substitutes. These include the need for small device sizes, patient growth requiring multiple reoperations, problems with enhanced calcification of bioprosthetic tissue, a perceived small market size, and a lack of sufficient patients to fill a typical clinical trial. These questions were addressed at a Paediatric Heart Valve Workshop held in Washington, DC on January 12, 2010 which was attended by clinicians, device industry representatives, academicians, and the US Food and Drug Administration. The following guidelines for *in vitro* testing of devices intended for the paediatric population are from a publication based on the workshop.

NOTE See Reference [41].

Some definitions of paediatrics include only four groups (new born, infant, child, adolescent), but input from paediatric clinicians led to adding the "toddler" subpopulation.

Table E.1 — Paediatric definitions

Paediatric subpopulation	Definition
Newborn	0 < age < 30 days
Infant	30 days ≤ age < 1 year
Toddler	1 year ≤ age < 5 years
Child	5 years ≤ age < 13 years
Adolescent	13 years ≤ age < 22 years

E.2 Pulsatile flow test conditions: left side

Table E.2 — Pulsatile flow test conditions: left side

Paediatric subpopulation	Systolic duration (%)	MAP (mmHg)	Beat rate (bpm)[a]	Cardiac output[a] (L/min)
Newborn	50	45	60, 150, 200	0,3; 1; 1,5
Infant	50	55	60, 120, 200	0,5; 2; 3
Toddler	45	65	60, 100, 160	1,5; 3; 4,5
Child	40	80	60, 80, 140	2; 3,5; 5
Adolescent	35	100	45, 70, 120	2, 5, 7

[a] Reference [41].

E.3 Pulsatile flow test conditions: right side

Table E.3 — Pulsatile flow test conditions: right side

Paediatric subpopulation	Systolic duration (%)	MAP (mmHg)	Beat rate (bpm)[a]	Cardiac output[a] (Lpm)
Newborn	50	20	60, 150, 200	0,3; 1; 1,5
Infant	50	20	60, 120, 200	0,5; 2; 3
Toddler	45	20	60, 100, 160	1,5; 3; 4,5
Child	40	20	60, 80, 140	2; 3,5; 5
Adolescent	35	20	45, 70, 120	2, 5, 7
[a] Reference [41].				

E.4 Steady back pressure and forward flow conditions: left side

Table E.4 — Steady back pressure and forward flow conditions: left side

Paediatric subpopulation	Steady back pressure[a] (mmHg)	Steady forward flow rates (Lpm)[a]
Newborn	40, 80	1,5; 3,5; 10
Infant	40, 80, 120	3,5; 10; 15
Toddler	40, 80, 120	5, 10, 15, 20
Child	40, 80, 120, 160	5, 10, 15, 20, 25
Adolescent	40, 80, 120, 160, 200	5, 10, 15, 20, 25, 30
[a] Reference [41].		

E.5 Steady back pressure and forward flow conditions: right side

Table E.5 — Steady back pressure and forward flow conditions: right side

Paediatric subpopulation	Steady back pressure[a] (mmHg)	Steady forward flow rates (Lpm)[a]
Newborn	5, 10, 20	1,5; 3,5; 10
Infant	5, 10, 20	3,5; 10; 15
Toddler	5, 10, 20	5, 10, 15, 20
Child	5, 10, 20, 30	5, 10, 15, 20, 25
Adolescent	5, 10, 20, 30, 40	5, 10, 15, 20, 25, 30
[a] Reference [41].		

E.6 Accelerated Wear Testing (AWT) conditions: left side

Table E.6 — AWT test conditions: left side

Paediatric subpopulation	Minimum mitral peak differential pressure[a] (mmHg)	Minimum aortic peak differential pressure[a] (mmHg)
Newborn	75	50
Infant	90	60
Toddler	97	67
Child	105	75
Adolescent	120	90

[a] Reference [41].

E.7 AWT test conditions: right side

Table E.7 — AWT test conditions: right side

Paediatric subpopulation	Minimum tricuspid peak differential pressure[a] (mmHg)	Minimum pulmonary peak differential pressure[a] (mmHg)
Newborn	30	10
Infant	30	10
Toddler	30	10
Child	30	10
Adolescent	30	10

[a] Reference [41].

E.8 FEA/life analysis conditions: left side

Table E.8 — FEA/life analysis conditions: left side

Paediatric subpopulation	FEA peak differential pressure/CO[a] (mmHg/Lpm)	Life analysis cycle criterion (equivalent years)
Newborn	90/1,5	5
Infant	100/3	7
Toddler	110/4,5	10
Child	135/5	10[b]
Adolescent	160/7	10[b]

[a] Reference [41].

[b] Reference [41] says 15 equivalent years, which comes from US FDA.

E.9 FEA/life analysis conditions: right side

Table E.9 — FEA/life analysis conditions: right side

Paediatric subpopulation	FEA peak Differential Pressure/CO[a] (mmHg/Lpm)	Life analysis cycle criterion (equivalent years)
Newborn	40/1,5	5
Infant	40/3	7
Toddler	40/4,5	10
Child	35/5	10[b]
Adolescent	40/7	10[b]

[a] Reference [41].

[b] Reference [41] says 15 equivalent years, which comes from US FDA.

Annex F
(informative)

Statistical procedures when using *in vitro* performance criteria

F.1 General

Historically, mean pressure difference and leakage values for a given valve size have been reported as the mean and standard deviation of three samples. Since these sample sizes are very small, they lead to wide confidence intervals when comparing results to a reference valve or performance criteria.

F.2 Methods

The confidence interval can be effectively reduced by modelling the entire experiment in a way that accounts for both the valve size and flow rate (for the pressure difference) or valve size and back pressure (for the leakage) (see Reference [35]). Suitable modelling methods include analysis of variance (ANOVA) and regression analysis. The performance criteria are then compared to the sample mean plus or minus a confidence interval. Additional information to report might include how well the model fits and the statistical significance of the effects of the size and flow rate (or back pressure). Note that if the same valve is tested under more than one condition (e.g. under several flow rates), then the multiple measurements should be taken into account to reflect the fact that the measurements on the same valve are not independent. In such cases, a nested ANOVA could be performed. This approach leads to smaller standard errors and narrower confidence intervals than the estimate obtained if the correlations among measurements are ignored.

Annex G
(informative)

Examples and definitions of some physical and material properties of heart valve systems

G.1 General

This Annex provides examples and definitions of the physical and material properties that could be relevant in characterizing a heart valve system and their definitions.

All measurements should be performed on materials or components as they would be found in the finished product. This includes all subsequent treatments after fabrication.

Examples of some standardized test methods that could be relevant for physical and material property characterization are provided in Annex H.

The risk analysis should play a role in the choice of determining the physical and material properties of the heart valve substitute and its components.

G.2 Bulk physical properties

G.2.1
biostability
change in chemical composition of a material after exposure to a physiologic-fluid environment

G.2.2
chemical composition
measurement of the chemical composition and purity including any processing aids

G.2.3
coefficient of thermal expansion
change in physical dimension as a result of a change in temperature

G.2.4
density
measurement of the mass per unit volume, i.e. the compactness of a material

G.2.5
film composition
analysis of the elemental composition of a film, expressed as a percentage

G.2.6
film thickness
thickness of a film deposited on a substrate averaged over the surface of the film

Note 1 to entry Techniques for measuring thin-film thickness include profilometry and ellipsometry. In some cases, Auger depth profiling can be used.

G.2.7
glass transition temperature
characteristic temperature of a polymer system below which long-chain mobility no longer exists

G.2.8
hydraulic expansion
comparison of the dimensions of the material before and after exposure to water

G.2.9
liquid diffusivity (porosity and permeability)
measurement of the ability of a material to absorb or adsorb biological components from the surrounding tissues and fluid environments

Note 1 to entry This biological property could cause calcification and premature failure of some animal tissues under certain stresses.

G.2.10
material hardness
measurement of resistance to scratching or plastic deformation by indentation (generally related to wear resistance)

G.2.11
melt index
number of grams of thermoplastic resin at a specified temperature that can be forced through a specified orifice in an allotted time by a specified pressure

G.2.12
melting point
temperature at which a solid material turns liquid

G.2.13
microstructure
measurement of the size and shape of the grains, defects, voids, etc. of which the material is composed. For tissue-derived materials, this should include, for example, cellular or collagen morphology

G.3 Surface physical properties

G.3.1 General

All measurements should be performed on materials or components as they would be found in the finished product. This includes all subsequent treatments after fabrication, for example, sterilization.

G.3.2
critical surface tension
surface morphology of a biological implant

Note 1 to entry Surface roughness and chemical composition play a key role on how an implant interacts with the biological host. Critical surface tension is a useful attribute for characterizing the surface of a solid material. The measurement is affected by the surface's topology, chemistry, and cleanliness. The measurements are related to the surface free energy of the material.

G.3.3
surface charge and surface charge density
type of charge (positive or negative) and the amount that can be bound to the surface of a material

Note 1 to entry It has been suggested that surface charge can play an important role in the biocompatibility of materials.

G.3.4
surface chemical composition
material composition within a few atomic layers of the surface

Note 1 to entry Variations in the chemicals present at the surface could affect how a material will react with the host. The chemical constituents of the surface can be altered by manufacturing processes such as grinding, polishing, cleaning, sterilizing, and handling.

G.3.5
surface resistance
R
ratio of the bulk resistivity and film thickness:

$$R_{\text{sheet}} = \frac{\Omega}{\delta}$$

where

Ω is the bulk resistivity, expressed in ohm-centimetres;

δ is the sample thickness, expressed in centimetres.

Note 1 to entry A typical method for determining the sheet resistance is the "four-point probe" method. Such measurements should be done at several places on the surface of the film to obtain an average sheet resistance value.

G.3.6
surface roughness
microtopology of the component surface

G.4 Mechanical and chemical engineering properties

G.4.1 General

The following are the materials engineering properties that can be evaluated to assess the ability of a material or a component to function in the intended site.

G.4.2
coefficient of friction
ratio of the force of friction to the normal force

G.4.3
compressive strength
stress required to deform a material in a uniaxial compressive stress state

Note 1 to entry There can be considerable variation in the measured strength among specimens in these tests. To ensure that the data are representative of the true strength of the material, the results should be reported using an appropriate statistical method.

G.4.4
corrosion fatigue
simultaneous action of cyclic stress and chemical attack on a metallic part

G.4.5
crack growth velocity
speed and load conditions under which a crack will propagate through a material once it has been initiated

Note 1 to entry The rates can be influenced by the residual stresses in the material.

G.4.6
creep
temporal change in dimension of a material under a prescribed mechanical loading condition

G.4.7
crevice corrosion
corrosion occurring in spaces (crevices) to which the access of the working fluid from the environment is limited

G.4.8
critical stress intensity factor
k_c
stress intensity above which a crack will advance under monotonic, quasi-static loading conditions; k_c is a function of the mode of loading, chemical environment, microstructure, test temperature, strain rate, and stress state

G.4.9
dynamic moduli
complex moduli (storage and loss moduli) that describe the mechanical behaviour of viscoelastic materials

G.4.10
fatigue
weakening of a material under cyclic loading (stress or strain)

G.4.11
fatigue life
number of cycles or total time a material can be repeatedly loaded without fracture under specified loading conditions

Note 1 to entry In general, there are two independent time components to fatigue failure. First is the crack initiation phase. When repeated loading cycles weaken a material, usually through a defect coalescence process at a flaw site until a critical flaw size is reached such that a crack is initiated. Once a crack is initiated, the second or crack growth phase of fatigue begins. The crack continues to grow under repeated loading conditions until the stress loading exceeds the fracture toughness resulting in total failure.

G.4.12
flexural strength
stress level required to cause fracture in bending

Note 1 to entry There usually is considerable variation in the measured strength among specimens in these tests. To ensure that the data are representative of the true strength of the material, the results should be reported using an appropriate statistical method.

G.4.13
fracture toughness
measure of the ability of a material to deform plastically in the presence of a notch

Note 1 to entry It is the stress intensity at which unstable crack growth will proceed.

G.4.14
fretting
surface damage that results when two surfaces in contact experience slight periodic relative motions

G.4.15
fretting corrosion
form of corrosion in which two surfaces rubbing against each other produce small particles which oxidize to form an abrasive powder that exacerbates the destructive process eventually forming a crack; the surface damage occurs between adjacent surfaces that are in close contact, under pressure, and are subjected to slight relative motions

G.4.16
galvanic corrosion
electrochemical process in which one metal corrodes preferentially when in electrical contact with a different metal and both metals are immersed in an electrolyte

G.4.17
general corrosion
uniform degradation of the surface of a metal due to chemical reactions with specific environments

G.4.18
intergranular corrosion
form of corrosion where the grain boundaries of a metal are more susceptible to corrosion than the matrix

G.4.19
peel strength
adhesion between different layers of a material usually a lamellar composite

Note 1 to entry Lamellae could include thin surface layers used to change the chemical boundary conditions of a material.

G.4.20
pitting corrosion
form of extremely localized corrosion that leads to the creation and propagation of small holes in the metal

G.4.21
Poisson's ratio
ratio of change in dimensions in the transverse direction to the longitudinal direction

Note 1 to entry When a piece of material is stretched or compressed longitudinally under a uniaxial load, it changes shape transversely. As with Young's modulus, Poisson's ratio is needed to model the mechanical behaviour of completed devices.

G.4.22
residual stress
stresses that remain in a material after it has been fabricated

G.4.23
strain energy to failure
energy needed to deform a material to the breaking point

Note 1 to entry Strain energy is a measure of the toughness of a material, generally, in the absence of a durability mechanism.

G.4.24
stress corrosion cracking
failure of a metal from the combined effects of a corrosion environment and a static tensile stress

G.4.25
stress intensity factor
k
description of the intensity of the stress field ahead of a sharp crack under linear elastic loading conditions

G.4.26
stress relaxation
gradual decrease in measured stress under a specified elongation or deformation

G.4.27
tear strength
force needed to initiate or continue tearing a sheet of fabric

G.4.28
tensile strain to failure (elongation)
total amount of strain or elongation that a material can tolerate just prior to fracture

G.4.29
tensile strength
stress required to deform a material in an uniaxial tensile stress state

Note 1 to entry The term "tensile strength" or "ultimate tensile strength" is usually used to define the load carrying capability of a material in a uniaxial tensile stress state typically expressed as an engineering stress. This condition also defines the limit of uniform strain after which plastic instability (necking) occurs.

Note 2 to entry There usually is considerable variation in the measured strength among specimens in these types of tests. To ensure that the data are representative of the true strength of the material, the results should be reported using an appropriate statistical method.

G.4.30
void concentration
number of voids in a film (areas where the film did not cover the substrate) per unit area

Note 1 to entry The void concentration is specific to the void size or range of sizes (e.g. a void concentration might be 100 voids of diameter 1 µm or less per square centimetre).

G.4.31
wear resistance
rate of the systematic removal of material as two surfaces move past one another

G.4.32
Young's modulus
slope of the initial linear portion of the stress strain curve; a measure of the mechanical stiffness of a material

Note 1 to entry As a tensile or compressive stress is exerted on a piece of material, it tends to elongate or contract. The ratio of the applied stress to the percentage change in length (strain) is defined as Young's modulus. Young's modulus is needed in theoretical modelling of both the static and dynamic stress distributions anticipated in completed devices.

G.5 Nitinol properties

G.5.1 General

Examples of nitinol properties are provided below. Figure G.1 gives an example of phase transformation of a nitinol alloy. Figure G.2 gives an example of a typical nitinol stress-strain curve. Figure G.3 gives an example of a nitinol crimping force-diameter curve.

G.5.2
austenite finish temperature
A_f
temperature at which the reverse martensite-to-austenite transformation is completed on heating in a single-stage transformation or the temperature at which the R-phase-to-austenite transformation is completed on heating in a two-stage transformation

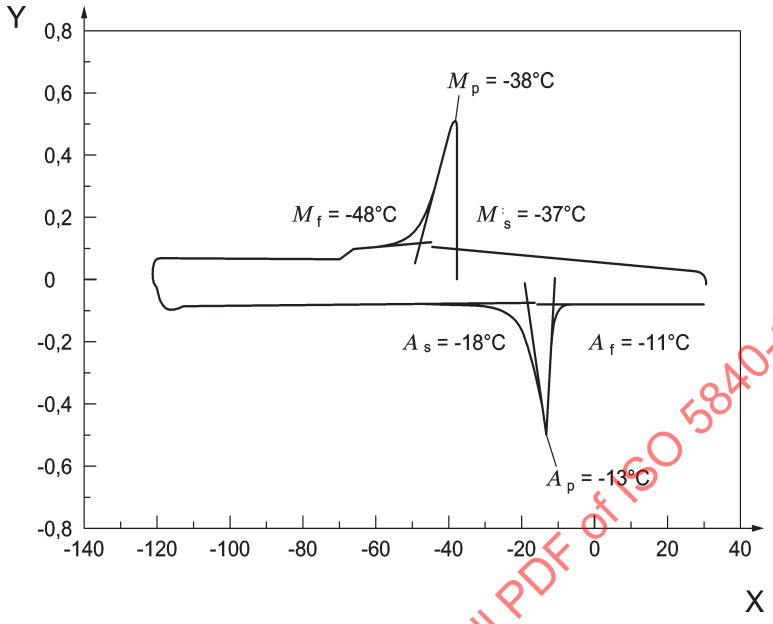
Note 1 to entry ASTM provides different methods for determining A_f (e.g. DSC or bend and free recovery).

G.5.2.1
bend and free recovery
test method to determine the A_f temperature of nitinol by measuring the rate of strain recovery as a function of temperature during heating of a previously deformed test sample

G.5.2.2
differential scanning calorimetry
DSC
technique in which the difference in heat flow into or out of a substance and an inert reference is

measured as a function of temperature while the substance and the reference material are subjected to a controlled temperature program

Note 1 to entry From ASTM F2005–05.



Key

X temperature (°C)
Y heat flow (W/g)
A_s Austenite start temperature
A_p Austenite peak temperature
A_f Austenite finish temperature
M_s Martensite start temperature
M_p Martensite peak temperature
M_f Martensite finish temperature

NOTE Reprinted from ASTM F2005 with permission of ASTM International.

Figure G.1 — Example DSC graph for single-stage transformation nickel-titanium alloy

G.5.3 Mechanical properties

G.5.3.1
austenite modulus
steepest part of the initial loading stress-strain curve of a superelastic nitinol sample; unlike most metals, the modulus of nitinol can exhibit significant temperature sensitivity and might be affected by the onset of a mechanically induced transition to the R-phase

G.5.3.2
lower plateau strength
LPS
stress at 2,5 % strain during unloading of the sample after loading to 6 % strain

Note 1 to entry See ASTM F2516 and Figure G.2.

G.5.3.3
martensite modulus
steepest part of the unloading stress-strain curve of a superelastic nitinol sample

G.5.3.4
residual elongation [%]
El_r
difference between the strain at a stress of 7,0 MPa during unloading and the strain at a stress of 7,0 MPa during loading

Note 1 to entry See ASTM F2516 and Figure G.2.

G.5.3.5
ultimate tensile strength
UTS
maximum load carrying capability of a sample tested in uniaxial tension

G.5.3.6
uniform elongation [%]
El_u
elongation at the maximum force sustained by the test piece just prior to necking, or fracture, or both

Note 1 to entry See ASTM F2516 and Figure G.2.

G.5.3.7
upper plateau strength
UPS
stress at 3 % strain during loading of the sample

Note 1 to entry See ASTM F2516 and Figure G.2.

G.5.4 Glossary of terms related to nitinol

G.5.4.1
austenite
high-temperature solid phase of approximately equiatomic composition in the Ni-Ti alloy system; after processing, to obtain specific properties, the austenite phase can undergo a reversible phase transformation to the martensitic or rhombohedral (R)-phases

G.5.4.2
chronic outward force
COF
force exerted by the support structure as it expands to its relaxed diameter after being radially compressed.

Note 1 to entry See Figure G.3.

G.5.4.3
martensite
low-temperature solid phase of approximately equiatomic composition in the Ni-Ti alloy system that formed from the austenite or the rhombohedral phase with either B19 (orthorombic) or B19' monoclinic crystal structure

G.5.4.4
nitinol
generic trade name for a Ni-Ti alloy (include typical composition range per ASTM) primarily used for its superelastic or shape memory behaviour

G.5.4.5
phase transformation
temperatures related to nitinol

G.5.4.5.1
martensite start temperature
M_s

temperature at which the forward austenite-to-martensite or R–phase-to-martensite transformation begins

G.5.4.5.2
martensite finish temperature
M_f
temperature at which the forward austenite-to-martensite or R–phase-to-martensite transformation ends

G.5.4.5.3
austenite start temperature
A_s
temperature at which the reverse martensite-to-austenite or R–phase-to-austenite transformation begins

G.5.4.5.4
rhombohedral (R-phase) start temperature
R_s
temperature at which the forward austenite-to-R–phase transformation begins

G.5.4.5.5
rhombohedral (R-phase) finish temperature
R_f
temperature at which the forward austenite-to-R–phase transformation ends

G.5.4.6
radial resistive force
RRF
force exerted by a superelastic nitinol support structure as it resists radial compression from its relaxed diameter

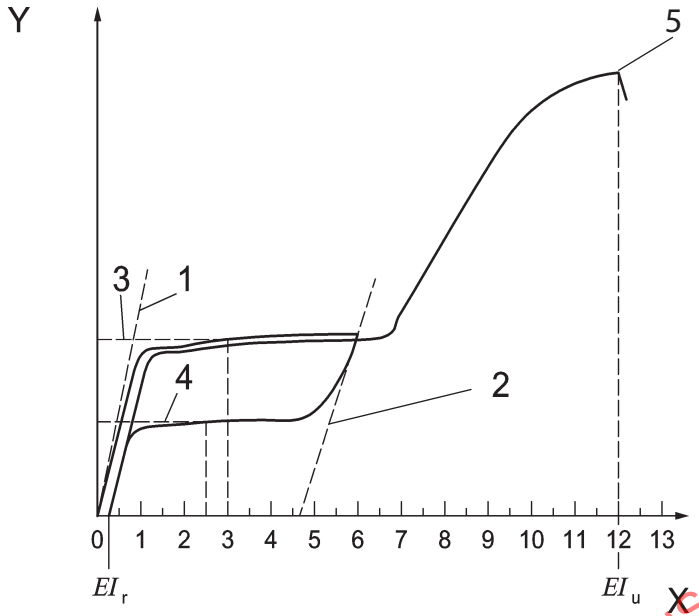
Note 1 to entry See Figure G.3.

G.5.4.7
rhombohedral (R) phase
metastable phase of nitinol

G.5.4.8
shape memory alloy
metal which after an apparent plastic deformation in the martensitic phase undergoes a thermoelastic phase transformation when heated through its transformation temperature range resulting in a recovery of the deformation

G.5.4.9
superelasticity
nonlinear recoverable deformation behaviour of Ni-Ti shape memory alloys at temperatures above the austenite finish temperature (A_f)

Note 1 to entry The nonlinear deformation arises from the stress induced formation of martensite on loading and the spontaneous reversion of this crystal structure to austenite upon unloading.

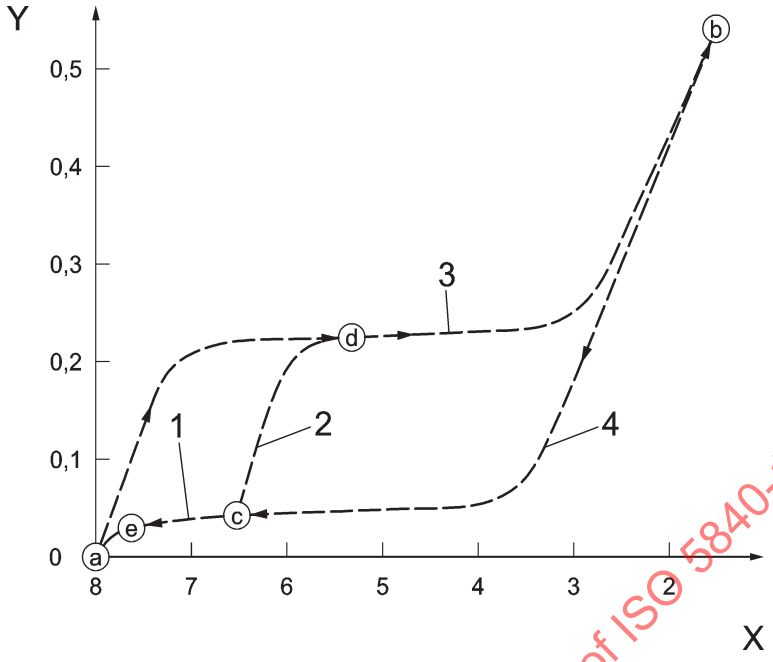


Key

1	Austenite modulus	X	strain (%)
2	Marstensite modulus	Y	stress
3	UPS	EI_r	residual elongation
4	LPS	EI_u	uniform elongation
5	UTS		

NOTE Reprinted from ASTM F2516 with permission of ASTM International.

Figure G.2 — Typical stress-strain curve of superelastic (SE) nitinol indicating various reportable parameters



Key

X	stent diameter (mm)
Y	hoop force (N/mm)
1 (b-c)	release from catheter, COF
2 (c-d)	RRF
3 (a-b)	loading: crimping into catheter
4 (c-e)	unloading

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Figure G.3 — Force-diameter curve of a superelastic (SE) nitinol support structure demonstrating chronic outward force (COF) and radial resistive force (RRF)

Annex H
(informative)

Examples of standards applicable to testing of materials and components of heart valve systems

H.1 Metals

H.1.1 Specifications for materials for metal surgical implants

ISO 5832-1, *Implants for surgery — Metallic materials — Part 1: Wrought stainless steel*

ISO 5832-2, *Implants for surgery — Metallic materials — Part 2: Unalloyed titanium*

ISO 5832-3, *Implants for surgery — Metallic materials — Part 3: Wrought titanium 6-aluminium 4-vanadium alloy*

ISO 5832-4, *Implants for surgery — Metallic materials — Part 4: Cobalt-chromium-molybdenum casting alloy*

ISO 5832-5, *Implants for surgery — Metallic materials — Part 5: Wrought cobalt-chromium-tungsten-nickel alloy*

ISO 5832-6, *Implants for surgery — Metallic materials — Part 6: Wrought cobalt-nickel-chromium-molybdenum alloy*

ISO 5832-7, *Implants for surgery — Metallic materials — Part 7: Forgeable and cold-formed cobalt-chromium-nickel-molybdenum-iron alloy*

ISO 5832-8, *Implants for surgery — Metallic materials — Part 8: Wrought cobalt-nickel-chromium-molybdenum-tungsten-iron alloy*

ASTM F2005, *Standard terminology for nickel-titanium shape memory alloys*

ASTM F2063, *Standard specifications for wrought nickel-titanium shape memory alloys for medical devices and surgical implants*

ASTM F2082, *Standard test method for determination of transformation temperature of nickel-titanium shape memory alloys by bend and free recovery*

ASTM F2004, *Standard test method for determination of transformation temperature of nickel-titanium shape memory alloys by thermal analysis*

ASTM F2516, *Standard test method for tension testing of nickel-titanium superelastic materials*

H.1.2 Tensile test with extensometer to failure

ASTM E8, *Standard test methods for tension testing of metallic materials*

ASTM E111, *Standard test method for young's modulus, tangent modulus, and chord modulus*

H.1.3 Poisson's ratio

ASTM E132, *Standard test method for poisson's ratio at room temperature*

H.1.4 Durability crack initiation and endurance limit; S-N curves

ASTM E466, *Standard practice for conducting constant amplitude axial fatigue test of metallic materials*

ASTM E468, *Standard practice for presentation of constant amplitude fatigue test results for metallic materials*

ASTM E739, *Standard practice for statistical analysis of linear or linearized stress-life (S-N) and strain-life (E-N) fatigue data*

H.1.5 Fatigue crack growth rate; crack growth velocity

ASTM E647, *Standard test method for measurement of fatigue crack growth rates*

H.1.6 Hardness

ISO 6508-1, *Metallic materials — Rockwell hardness test — Part 1: Test method (scales A, B, C, D, E, F, G, H, K, N, T)*

ISO 6507-1, *Metallic materials — Vickers hardness test — Part 1: Test method*

H.1.7 Microstructure

ASTM E3, *Standard guide for preparation of metallographic specimens*

ASTM E112, *Standard test methods for determining average grain size*

H.1.8 Thermal expansion

ASTM E228, *Linear thermal expansion of solid materials with a vitreous silica dilatometer*

H.1.9 Fracture toughness

ASTM E399, *Standard test method for plane-strain fracture toughness of metallic materials*

ASTM E1820, *Standard test method for measurement of fracture toughness*

H.1.10 Fatigue life

ASTM E466, *Standard practice for conducting force controlled constant amplitude axial fatigue tests of metallic materials*

ASTM E468, *Standard practice for presentation of constant amplitude fatigue test results for metallic materials*

ASTM E739, *Standard practice for statistical analysis of linear or linearized stress-life (S-N) and strain-life (E-N) fatigue data*

H.1.11 Corrosion

ASTM F2129, *Standard test method for conducting cyclic potentiodynamic polarization measurements to determine the corrosion susceptibility of small implant devices*

ASTM G46, *Standard guide for examination and evaluation of pitting corrosion*

ASTM F746, *Standard test method for pitting or crevice corrosion of metallic surgical implant materials*

ASTM G61, *Standard test method for conducting cyclic potentiodynamic polarization measurements for localized corrosion susceptibility of iron-, nickel-, or cobalt-based alloys*

ASTM F746, *Standard test method for pitting or crevice corrosion of metallic surgical implant materials*

ASTM G192-08, *Standard test method for determining the crevice repassivation potential of corrosion-resistant alloys using a potentiodynamic-galvanostatic-potentiostatic technique*

ASTM G82, *Standard guide for development and use of a galvanic series for predicting galvanic corrosion performance*

ASTM G71, *Standard guide for conducting and evaluating galvanic corrosion tests in electrolytes*

ASTM G106-89, *Standard practice for verification of algorithm and equipment for electrochemical impedance measurements*

ASTM G161-00, *Standard guide for corrosion-related failure analysis*

ASTM G199–09, *Standard guide for electrochemical noise measurement*

ASTM G108, *Standard test method for electrochemical reactivation (epr) for detecting sensitization of aisi type 304 and 304l stainless steels*

ASTM G44, *Standard practice for exposure of metals and alloys by alternate immersion in neutral* 3,5 *% sodium chloride solution*

ASTM A262, *Standard practices for detecting susceptibility to intergranular attack in austenitic stainless steels*

ASTM F1801-97, *Standard practice for corrosion fatigue testing of metallic implant materials*

ISO 16429, *Implants for surgery — Measurements of open-circuit potential to assess corrosion behaviour of metallic implantable materials and medical devices over extended time periods*

H.2 Polymers

H.2.1 Viscosimetry

ASTM D20, *Standard test method for distillation of road tars*

ISO 61, *Plastics — Determination of apparent density of moulding material that cannot be poured from a specified funnel*

H.2.2 Melt flow index

ASTM D1238, *Standard test method for melt flow rates of thermoplastics by extrusion plastometer*

H.2.3 Specifications for high molecular weight polyethylene

ISO 3834-1, *Quality requirements for fusion welding of metallic materials — Part 1: Criteria for the selection of the appropriate level of quality requirements*

ISO 3834-2, *Quality requirements for fusion welding of metallic materials — Part 2: Comprehensive quality requirements*

ISO 3834-3, *Quality requirements for fusion welding of metallic materials — Part 3: Standards quality requirements*

ISO 3834-4, *Quality requirements for fusion welding of metallic materials — Part 4: Elementary quality requirements*

H.2.4 Determination of breaking strength under static load

ISO 13934-1, *Textiles — Tensile properties of fabrics — Part 1: Determination of maximum force and elongation at maximum force using the strip method*

H.2.5 Tensile test with extensometer to failure (if possible)

ASTM D638, *Standard test method for tensile properties of plastics*

H.2.6 Tensile properties

ISO 527 (all parts), *Plastics — Determination of tensile properties*

H.2.7 Poisson's ratio

ASTM E132, *Standard test method for Poisson's ratio at room temperature*

H.2.8 Determination of dynamic mechanical properties

ISO 6721-1, *Plastics — Determination of dynamic mechanical properties — Part 1: General principles*

ISO 6721-2, *Plastics — Determination of dynamic mechanical properties — Part 2: Torsion-pendulum method*

H.2.9 Resistance to surface wear

ISO 4586-2, *High-pressure decorative laminates — Sheets made from thermosetting resins — Part 2: Determination of properties*

H.2.10 Resistance to scratch

ISO 1518-1, *Paints and varnishes — Determination of scratch resistance — Part 1: Constant-loading method*

BS 3962-6, *Assessment of resistance to mechanical damage*

H.2.11 Flexural properties; determination of breaking strength under dynamic bending load

ISO 178, *Plastics — Determination of flexural properties*

H.2.12 Fatigue crack initiation and endurance limit; S-N curves

ASTM E466, *Standard practice for conducting force controlled constant amplitude axial fatigue tests of metallic materials*

ASTM E468, *Practice for presentation of constant amplitude fatigue test results for metallic materials*

H.2.13 Fatigue crack growth rate

ASTM E647, *Test method for measurement of fatigue crack growth rates*

H.2.14 Determination of compressive properties

ISO 604, *Plastics — Determination of compressive properties*

H.2.15 Specification of surgical implants made from high-density silicone elastomer

BS 7253-3, *Non-metallic materials for surgical implants — Specification for surgical implants made of heat-vulcanized silicone elastomer*

H.2.16 Density

ASTM E792, *Standard guide for selection of a clinical laboratory information management system*

H.2.17 Liquid diffusivity (porosity and permeability; water absorption)

ASTM D570, *Standard test method for water absorption of plastics*

H.2.18 Hardness

ASTM D785, *Standard test method for rockwell hardness of plastics and electrical insulating materials*

H.2.19 Wear resistance

ASTM D1044, *Standard est methods for resistance of transparent plastics to surface abrasion*

ASTM D4060, *Standard test method for abrasion resistance of organic coatings by the taber abraser*

H.2.20 Creep

ASTM D2990, *Test methods for tensile, compressive, and flexural creep and creep-rupture of plastics*

H.2.21 Fracture toughness

ASTM E399, *Standard test method for plane-strain fracture toughness of metallic materials*

ASTM E1820, *Standard test method for measurement of fracture toughness*

H.2.22 Hydraulic expansion

ASTM F1087, *Test methods for linear dimensional stability of a gasket material to moisture*

H.3 Ceramics and carbons

H.3.1 Physical and chemical properties

ISO 6474-1, *Implants for surgery — Ceramic materials — Part 1: Ceramic materials based on high purity alumina*

H.3.2 Fatigue rate

ASTM E647, *Standard test method for measurement of fatigue crack growth rates*

H.3.3 Hardness

ASTM E92, *Standard test method for vickers hardness of metallic materials*

H.3.4 Thermal expansion

ASTM E228, *Linear thermal expansion of solid materials with a vitreous silica dilatometer*

H.3.5 Fracture toughness

ASTM E399, *Standard test method for plane-strain fracture toughness of metallic materials*

H.4 Biological materials

H.4.1 Possible adaptation of tensile properties

ISO 527 (all parts), *Plastics — Determination of tensile properties*

H.5 Textiles

H.5.1 Determination of tear-out resistance

ISO 13937-2, *Textiles — Tear properties of fabrics — Part 2: Determination of tear force of trouser-shaped test specimens (Single tear method)*

H.5.2 Determination of water absorption

DIN 53923, Testing of textiles — Determination of water absorption of textile fabrics

H.6 MRI compatibility

ASTM F2052, *Standard test method for measurement of magnetically induced displacement force on medical devices in the magnetic resonance environment*

ASTM F2119, *Standard test method for evaluation of MR image artefacts from passive implants*

ASTM F2182, *Standard test method for measurement of radio frequency induced heating near passive implants during magnetic resonance imaging*

ASTM F2213, *Standard test method for measurement of magnetically induced torque on medical devices in the magnetic resonance environment*

ASTM F2503, *Standard practice for marking medical devices and other items for safety in the magnetic resonance environment*